Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. Reply

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DOI: https://doi.org/10.1056/NEJMc1910735

Although there were only 7 patients with *FGFR2* fusion in our trial, none of whom had an objective response, we note that the disease control rate in this group was 71%, which is similar to that in the overall trial population. Having said that, more information is needed to understand the clinical benefit of erdafitinib both in patients with no history of chemotherapy and in those with *FGFR* alterations.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2018;174:1033.
2. Joerger M, Cassier PA, Penel N, et al. Rogaratinib in patients with advanced urothelial carcinomas prescreened for tumor FGFR mRNA expression and effects of mutations in the FGFR signaling pathway. J Clin Oncol 2018;36:Suppl:4513. abstract.
3. Wang L, Gong Y, Saci A, et al. Fibroblast growth factor receptor 3 alterations and response to PD-1/PD-L1 blockade in patients with metastatic urothelial cancer. Eur Urol 2019 July 1 (Epub ahead of print).

DOI: 10.1056/NEJMc1911187

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

TO THE EDITOR: In the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, Distler et al. (June 27 issue)[1] report that the annual rate of decline in forced vital capacity in patients with interstitial lung disease (ILD) associated with systemic sclerosis was lower among those who received nintedanib than among those who received placebo. The answers to several important questions would better define to whom this result applies. Are the patients who have more fibrosis than ground-glass opacities on high-resolution computed tomographic (CT) scans the ones who will benefit the most from nintedanib, as shown in trials involving patients with idiopathic pulmonary fibrosis?[2] Is the effect of nintedanib similar in patients with a predominant ground-glass pattern on high-resolution CT scans and in those with a predominant fibrotic pattern? Is the effect of nintedanib, given its antiinflammatory properties in preclinical trials,[3] similar to that of mycophenolate in patients with predominantly ground-glass opacities? We hope that the authors can provide clinicians with this information to better characterize the type of patients with ILD associated with systemic sclerosis who will benefit the most from nintedanib.

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Dr. Moran-Mendoza reports having received honoraria from Boehringer Ingelheim and Hoffmann–La Roche for participation in advisory boards and educational activities, as well as financial support for his ILD nurse, and having collaborated in research studies for Boehringer Ingelheim and Hoffmann–La Roche. No other potential conflict of interest relevant to this letter was reported.

1. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis–associated interstitial lung disease. N Engl J Med 2019;380:2518-28.
2. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
3. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther 2014;349:209-20.

DOI: 10.1056/NEJMc1910735

TO THE EDITOR: Distler et al. showed that nintedanib has an antifibrotic effect in patients with ILD associated with systemic sclerosis. Apparently, nintedanib did not reduce extrapulmonary manifestations of systemic sclerosis. However, in

many cases, nintedanib caused diarrhea, nausea, vomiting, or weight loss. This prompts the question of whether the patients had any overall improvement.

Systemic sclerosis is a disease in which gastrointestinal manifestations are common, resulting in a decreased quality of life.[1] Weight loss may be rapid and difficult to manage and is associated with poor survival.[2] More precise information on the gastrointestinal toxicity of nintedanib would be valuable. What are the data on weight loss and gastrointestinal morbidity? Furthermore, we would have liked to learn which adverse effects led to drug withdrawal in the 46 of 288 patients who received nintedanib, such as was reported in the INPULSIS trial.[3] If nintedanib attenuates the decline of the forced vital capacity in patients with systemic sclerosis at the expense of worsened gastrointestinal morbidity, then the overall benefit for such patients remains to be proven.

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No potential conflict of interest relevant to this letter was reported.

1. Shreiner AB, Murray C, Denton C, Khanna D. Gastrointestinal manifestations of systemic sclerosis. J Scleroderma Relat Disord 2016;1:247-56.
2. Richard N, Hudson M, Wang M, et al. Severe gastrointestinal disease in very early systemic sclerosis is associated with early mortality. Rheumatology (Oxford) 2019;58:636-44.
3. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.

DOI: 10.1056/NEJMc1910735

THE AUTHORS REPLY: In reply to Moran-Mendoza et al.: patients were eligible for inclusion in the SENSCIS trial if they had features consistent with ILD associated with systemic sclerosis on a high-resolution CT scan, with an extent of fibrotic interstitial lung disease of at least 10%. Among the patients with available data, 42 of 283 (14.8%) in the nintedanib group and 36 of 282 (12.8%) in the placebo group did not have ground-glass opacities on high-resolution CT. Post hoc analyses showed no heterogeneity in the treatment effect of nintedanib as compared with placebo on the rate of decline in forced vital capacity in subgroups defined according to the presence or absence of ground-glass opacities (P>0.05 for treatment-by-time-by-subgroup interaction). To date, no heterogeneity has been found in the treatment effect of nintedanib in subgroups defined according to a variety of baseline characteristics, which suggests that nintedanib is effective in reducing the progression of ILD associated with systemic sclerosis across a broad population of patients. However, we caution against overinterpreting multiple subgroup analyses as a means of identifying independent predictors of treatment response.

In reply to Andréasson et al.: in the SENSCIS trial, diarrhea, nausea, and vomiting were the most frequent adverse events among the patients who received nintedanib and were the adverse events that most frequently led to treatment discontinuation. However, nintedanib was discontinued prematurely by only 20 patients (6.9%) because of diarrhea, 6 patients (2.1%) because of nausea, and 4 patients (1.4%) because of vomiting; these outcomes suggest that the guidance provided to investigators on the management of adverse events through the use of antidiarrheal treatment, hydration, and dose adjustment was effective in enabling patients to continue treatment. Weight loss was reported as an adverse event in 34 patients (11.8%) in the nintedanib group and in 12 patients (4.2%) in the placebo group and led to discontinuation of the trial drug in 1 patient in the nintedanib group. Andréasson et al. raise the question of the ratio of risk to benefit. We believe that nintedanib provides a benefit in patients with ILD associated with systemic sclerosis by reducing the rate of progression of interstitial lung disease, which is the leading cause of death in these patients.[1] Our data show that the side effects of nintedanib did not result in treatment discontinuation in most patients.

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Since publication of his article, Dr. Distler reports receiving fees for project scoring from Pfizer. No further potential conflict of interest relevant to this letter was reported.

1. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897-905.
DOI: 10.1056/NEJMc1910735

New Guidelines for Statistical Reporting

TO THE EDITOR: Harrington et al. (July 18 issue)[1] describe new guidelines for statistical reporting in the *Journal.* One important change is that P values may not be reported if a method for adjustment for multiple hypothesis testing was not prespecified. Assuming there is complete reporting of all tests that were conducted, this policy appears to address a concern that investigators may select a method that yields the most favorable results (e.g., one that maximizes the number of adjusted P values <0.05 or minimizes the minimum adjusted P value). We investigated these strategies in simulation studies using six methods that control family-wise error (Bonferroni, Holm, Hommel, Hochberg, Sidak single-stage, and Sidak step-down) and three that control false discovery rates (Benjamini–Hochberg, Benjamini–Yekutieli, and two-stage Benjamini–Hochberg). Both of the post hoc adjustment strategies, which involve a high degree of selection, maintain an equivalent level of control of the family-wise error rate under a range of number of tests and correlations Table 1). This is not the case when the adaptive Benjamini–Hochberg method is included. In conjunction with appropriate presentation of estimates and confidence intervals, the *Journal* might allow post hoc testing with the use of these nine methods.

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No potential conflict of interest relevant to this letter was reported.

1. Harrington D, D'Agostino RB Sr, Gatsonis C, et al. New guidelines for statistical reporting in the *Journal.* N Engl J Med 2019;381:285-6.

DOI: 10.1056/NEJMc1911817

THE AUTHOR REPLIES: Betensky and Newberger's simulation shows that when a set of comparisons (i.e., a family of tests) is well defined in advance, the arbitrary choice of a post hoc procedure may not lead to inflated type 1 or false discovery probabilities. Their assumption requires that the comparisons shown in a manuscript be the only ones examined for possible inclusion.

Betensky and Newberger's proposal presents some operational challenges as well. Many studies in the medical literature aim to provide evidence

Table 1. Estimated Family-wise Error Rate (10,000 Repetitions) under a Complete Null Hypothesis.*

No. of Tests and Correlations	Procedures Used		
	Family-wise Error Rate	False Discovery Rate	All
20			
Correlation			
0	0.052	0.052	0.053
0.5	0.032	0.037	0.037
0.9	0.019	0.026	0.026
50			
Correlation			
0	0.046	0.046	0.047
0.5	0.029	0.034	0.034
0.9	0.015	0.025	0.025
100			
Correlation			
0	0.051	0.052	0.053
0.5	0.027	0.034	0.034
0.9	0.010	0.022	0.022

* For each replication, post hoc procedures were chosen that either maximized the number of adjusted P values <0.05, or equivalently, minimized the minimum adjusted P value, simulating a setting in which the data analyst chooses the most favorable approach. Each replicate simulated P values from cumulative, normal, distribution-function transformations of equicorrelated multivariate standard normal distributions. Family-wise error rate procedures include Bonferroni, Hochberg, Hommel, Sidak single-stage, and Sidak step-down. False-discovery rate procedures include Benjamini–Hochberg, Benjamini–Yekutieli, and two-stage Benjamini–Hochberg. The simulation used the mt.rawp2adjp function in a multiple-test package in Bioconductor and the p.adjust function in R (Hommel procedure only).